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10/672,266	09/25/2003	Byung Sook Moon	020048-004200US	8805

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EXAMINER

PANDE, SUCHIRA

ART UNIT

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1637

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/672,266

**Applicant(s)**

MOON ET AL.

**Examiner**

SUCHIRA PANDE

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-64 is/are pending in the application.
- 4a) Of the above claim(s) 11, 13-44, 49 and 54-62 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10, 12, 45-48, 50-53 and 63-64 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_

- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## DETAILED ACTION

### Claim Status

1. Amendment filed on January 30, 2008 is acknowledged. Applicant amended claims 1, 9, 45, and 51; withdrew claims 11, 13-44, 49, 54-62; and added two new claims 63 and 64. Consequently claims 1-10, 12, 45-48, 50-53 and 63-64 are pending and will be examined in this action.

### ***Response to Amendment and claim interpretation***

2. Applicant has amended the base claim 1 and 45 by adding a shape limitation "being substantially spherical in shape" to the claimed beads.

Applicant has not defined "substantially spherical" in the specification. Fig. 1 part A of the specification shows beads that are made with 9% w/v = 72% w/w of Trehalose. To the Examiner these beads shown in Fig. 1 A, appear to be "substantially spherical in shape". Based on this Examiner concludes, lyophilized beads made with sugars other than mannitol and having w/w percentages that are within the claimed range of mannitol are also "substantially spherical in shape".

Therefore the lyophilized beads taught by Park and Trembl will still meet the newly added limitation i.e. they will also be "substantially spherical in shape". Hence Examiner concludes that the cited art is still applicable and the amendment is not sufficient to overcome the cited art.

In addition, Examiner searched the specification of application as filed to find support for the newly added limitation namely "substantially spherical". Examiner did not come across single instant where term substantially was used

in this context. Hence Examiner is doing a written description new matter rejection to indicate the above fact.

**Response to Applicant's submission of 37 CFR 1.132 Declaration**

3. The declaration by Martin Jones under 37 CFR 1.132 filed on July 12, 2007 is insufficient to overcome the rejection of claims 1-8, 10, 12, 45-48, 50 and 52-53 based upon Park and Trembl as set forth in the last Office action because: The declaration filed by Martin Jones provides details of unexpected results but the unexpected results described in the declaration from paragraph 5-9 are related to features of lyophilized "crystalline beads". Again Examiner would like to point out that structural limitation "crystalline beads" are not part of the current claim language. Hence unexpected results provided by Martin Jones that relate to features that are not recited in the instant claim language of the product claimed, are insufficient to overcome the rejection of claims 1-8, 10, 12, 45-48, 50 and 52-53 based upon Park and Trembl as set forth in the last Office action. Hence these are being maintained.

Response to Applicant's arguments re rejection under 103(a) of claims 1-8, 10, 12, 45-48, 50 and 52-53 and 63-64 over Park and Trembl.

4. Examiner would like to note that Applicant has amended base claims 1 and 45 in an effort to advance prosecution however newly added claims 63 and 64 are verbatim copies of the claims 1 and 45 respectively that were rejected in office action mailed on 7/31/2007. Hence newly added claims 63 and 64 are being rejected using exact same grounds of rejection that were previously cited for claims 1 and 45 in the in office action mailed on 7/31/2007.

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Response to Applicant's arguments re rejection under 103(a) of claims 8 and 50 over Park, Tremi and Kellogg and claims 9 and 51 over Park, Tremi and Shively.

5. Since 103 (a) rejections over Park and Tremi have been maintained the rejections of claims further in view of other secondary references Kellogg and Shively respectively are also being maintained.

Routine Optimization

6. During the interview of June 4, 2007 a consensus was reached that Tremi does not disclose compositions having mannitol concentrations in the range between about 53% and 75%. The compositions of Tremi et al. were shown to contain about 45% mannitol. Thus, an ordinary practitioner would have recognized that the results optimizable variables of concentration of mannitol could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific mannitol concentration was other than routine, that the products resulting from the optimization have any unexpected claimed properties, or that the beads made by the instant invention should be considered unexpected in any way with reference to their suitability for amplification of nucleic acid as compared to the closest prior art.

***Claim Rejections - 35 USC § 112***

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7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10, 12, 45-48, 50-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Regarding claims 1 and 45 applicant has added the limitation "substantially spherical". Examiner could not find even a single instance in the specification where term substantial or substantially was used in context of the spherical lyophilized beads. Therefore a NEW MATTER rejection is being made for claims 1 and 45. Claims 2-10, 12, 46-48, 50-53 depend from claims 1 and 45. Hence the NEW MATTER rejection applies to claims 1-10, 12, 45-48, and 50-53.

### ***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-7, 10, 12, 45-48, 52-53, 63 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. 1999 US Pat. 5,861,251 in view of Trembl et al. 1998 US Pat. 5,763,157.

Claims 1, 45, 63 and 64 are being considered together because claims 45 and 64 are a product by process claim that shares the same structural components namely lyophilized bead suitable for use in amplification of a nucleic acid comprising a thermally stable enzyme and mannitol as recited in product of claims 1 and 63. The process steps (a-c in claim 45) are not being considered for search of prior art. See MPEP 2113 [R1] PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the

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product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.”

A) Regarding claims 1, 7, 45, 48, 63 and 64 Park et al. teach:

- a. A lyophilized reagent suitable for use in the amplification of a nucleic acid sequence, (see col. 1, lines 5-10, and col. 3, lines 1-10)
- b. said lyophilized reagent comprising: a thermally stable enzyme (see col. 3, lines 1-10). Park et al. teach use of DNA Polymerase as the enzyme used for conducting amplification of nucleic acid using polymerase chain reaction where the enzyme is subjected to repeated cycling at high temperatures up to 94°C. Hence the DNA polymerase used by them is thermally stable as it successfully performs DNA amplification as shown in examples 1-8 (see col. 3, lines 66-67; col. 4, 5 and 6 lines 1-67 of each).
- c. And mannitol (see col. 3, line 27). Park et al. use mannitol as a stabilizer. Mannitol is part of their preferred stabilizers falling in the group of polyols composed of glycerol, glucose, mannitol, galactitol, glucitol and sorbitol (see col. 3, lines 24-30).

Regarding claim 2, Park et al. teaches amplification in a reaction mixture having a final volume of 50 µl (see col. 4, lines 12-13 and lines 47-52).

Regarding claims 3 and 47, Park et al. teaches dNTPs (see col. 4, line 11) and mixture of ddNTPs and dNTPs (see col. 3, lines 1-10).

B) Regarding claims 1, 45, 63 and 64 Park et al. do not teach:



- d. A lyophilized bead wherein said lyophilized bead has a weight percentage of said mannitol of between about 53% and about 75% (w/w).
- C) Regarding claims 1, 5-6, 45, 63 and 64 Trembl et al. teach:

e. A lyophilized bead referred to as biological reagent spheres by Trembl et al. suitable for use in the amplification of a nucleic acid sequence (see col. 3, lines 60-67; col. 4, lines 1-8 & col. 7, lines 23-35).

In case of Trembl et al. these beads are composed of a high molecular weight synthetic carbohydrate polymer and a second carbohydrate. Examples of second carbohydrate used by Trembl et al. includes polyols such as sorbitol. The lyophilized beads with weight percentage of second carbohydrate in the range of 5% to 15% expressed in (w/v) are taught by Trembl et al. (see col. 5, lines 49-52). Trembl et al. does not express the weight percentage of polyol in the beads in (w/w).

During interview of June 4, 2007 consensus was reached that Trembl does not disclose compositions in the range between 53% and about 75%. The range disclosed by Trembl would be about 45% (w/w).

Therefore lyophilized beads of claims 1, 5, 6, 63 having weight percentage of between about 53% and about 75% (w/w) as recited in claims 1 and 63; weight percentage of lyophilized bead between about 62% and about 75% (w/w) as recited in claim 5; and weight percentage of lyophilized bead between about 68% and about 75% (w/w) as recited in claim 6 are not taught by Trembl et al.

The compositions of Trembl et al. were shown to contain about 45% (w/w) polyol .

Thus, an ordinary practitioner would have recognized that the results optimizable

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variables of concentration of mannitol could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific mannitol concentration was other than routine, that the products resulting from the optimization have any unexpected claimed properties, or that the beads made by the instant invention should be considered unexpected in any way with reference to their suitability for amplification of nucleic acid as compared to the closest prior art.

Regarding new limitation added to amended base claim 1 and 45 that recites lyophilized beads "being substantially spherical in shape". Applicant has not defined "substantially spherical" in the specification. Fig. 1 part A of the specification shows beads that are made with 9% w/v = 72% w/w of Trehalose. To the Examiner these beads shown in Fig. 1 A, appear to be "substantially spherical in shape". Based on this Examiner concludes, since lyophilized beads made with sugars other than mannitol and having w/w percentages that are within the claimed range are also "substantially spherical in shape".

Therefore the lyophilized beads taught by Park and Tremblé et al. will necessarily meet the newly added limitation i.e. they will also be "substantially spherical in shape".

Regarding claims 4 and 46, Trembl et al. teaches reagent spheres (lyophilized beads) with diameters of about 2 mm to about 6 mm. Preferably, the reagent sphere has a diameter of about 2.5 mm (see col. 3, lines 63-65). Thus lyophilized bead with an average cross-section of about 1 mm and about 4.5 mm are taught by Trembl et al.

Regarding claims 10 and 52, Trembl et al. teaches reagent spheres where the biological reagents are oligonucleotides, proteins, enzymes, DNA or nucleic acids (see col. 4, lines 7-8). All of these are employed as probes in the art for different purposes.

Regarding claims 12 and 53, Trembl et al. teaches reagent spheres where the biological reagent is selected from at least one of the group consisting of DNA/RNA modifying enzymes, restriction enzymes, nucleotides, oligonucleotides, proteins, enzymes, DNA or nucleic acids (see col. 4, lines 4-8). Different molecules may be used as internal control for different purposes. For example DNA could be used as internal control for amplification reactions, therefore Trembl et al. teaches a bead containing internal control.

As described above Park et al specifically teach use of mannitol as a preferred polyol to be used for stabilizing lyophilized reagents to be used for nucleic acid amplification.

Hence it would have been obvious to one of ordinary skill in the art at the time of the present invention to use the lyophilized beads of Trembl et al. as the lyophilized reagent of Park et al. for use in nucleic acid amplification. The motivation to use lyophilized beads as described by Trembl et al. as lyophilized

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reagent useful for amplification of nucleic acid taught by Park et al. is provided by Trembl et al. who describe the limitations and drawbacks associated with the various methods such as dry-blending, spray drying, freeze drying, fluidized bed drying, and /or cryogenic freezing employed for producing dry biological reagents (see col. 1, lines 32-67; col. 2, lines 1-25; col. 3, lines 1-22). They further go on to describe the advantages of their invention namely "providing a homogenous solution of biological reagent(s), glass forming filler material, and water-wherein the shape of droplets formed on an inert cryogenic surface can be controlled by changing the percent solids of emulsion -----providing stable storage of a biological reagent that would otherwise be unstable when alone in an aqueous solution at room temperature and providing stable storage of a plurality of biological reagents that would otherwise react with each other when in an aqueous solution at room temperature" (see col.4, lines 51-67 and col. 5, lines 1-9).

9. Claims 8 and 50, are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. and Trembl et al. as applied to claims 1 and 45 above, and further in view of Kellogg et al. (1994) Biotechniques Vol. 16 (6) 1134-1137.

Regarding claims 8 and 50, Park et al. and Trembl et al. teach the bead of claim 1 and 45 but they do not teach a component selected from the group consisting of an antibody that inactivates a polymerase and a wax or oil to sequester magnesium.

Regarding claims 8 and 50, Kellogg et al. teach an antibody that inactivates a polymerase (see page 1135, par. 3 where a Taq DNA Polymerase that when coupled to neutralizing TaqStartAntibody<sup>TM</sup>, a monoclonal antibody (MAb) directed against Taq DNA polymerase facilitates "Hot start" PCR is taught)

It would have been prima facie obvious to one of ordinary skill in the art to incorporate the Taq DNA Polymerase coupled to neutralizing TaqStartAntibody<sup>TM</sup>, of Kellogg et al. in the product of Park et. al. and Trembl et al. at the time the invention was made. The motivation to combine the product of Kellogg et al. in the product of Park et al. and Trembl et al. is provided by Kellogg et al. who state "To address the drawbacks inherent in the above methods, we have generated the TaqStartAntibody<sup>TM</sup>, a monoclonal antibody (MAb) the deactivates Taq DNA polymerase at ambient temperature. Heating a reaction mixture to the denaturation temperature reverses the deactivation of the polymerase and permits the amplification to proceed in a specific and efficient manner. The results indicate that using the antibody greatly reduces non specific products and enhances yield of the specific product" (see page 1135, par. 3).

10. Claims 9 and 51, are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. and Trembl et al. as applied to claims 1 and 45 above, and further in view of Shively et al. March 2003 BioTechniques vol. 34: (3) pp. 498-504.

Regarding claims 9 and 51, Park et al. teaches a reaction buffer (see col. 2, line 1) that must be part of the reaction mixture before amplification of nucleic acids can take place by PCR. But neither Park et al. nor Trembl et al. teaches use of

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buffer N-(2-Hydroxyethyl) piperazine-N'-(2-ethanesulfonic acid) (HEPES) in DNA amplification.

Shively et al. teaches use of HEPES buffer in amplification reactions used to perform Real –Time PCR assay for quantitative mismatch detection. (see page 498 abstract). They describe an assay suitable for quantitative detection of single-base-pair differences that does not require fluorescently labeled gene specific probes. The method requires use of HEPES buffer at a pH of 6.95 together with Ampli-Taq<sup>R</sup> DNA polymerase results in a threshold difference between the correct template and the mismatched template of as many as 20 cycles, depending on the mismatch. (see page 498, abstract).

It would have been obvious to one of ordinary skill in the art to incorporate the buffer of Shively et al. in the product of Park et al. and Trembl et al. The motivation to combine the buffer of Shively et al. in the product of Park et al. and Trembl et al. is provided by Shively et al. who state “ the technique we describe allows more accurate quantification because the buffer we utilize results in greater allele-specific differences in threshold cycles (see page 499, par. 1)” and “It was necessary to use HEPES buffer, pH 6.95, instead of the standard Tris-HCl, pH 8.3, for mismatch discrimination at the level shown in Figure 2”. (see page 502, par. 3).

### ***Conclusion***

12. All claims under consideration 1-10, 12, 45-48, 50-53, 63 and 64 are rejected over prior art. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE**

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**FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande  
Examiner  
Art Unit 1637

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April 3, 2008